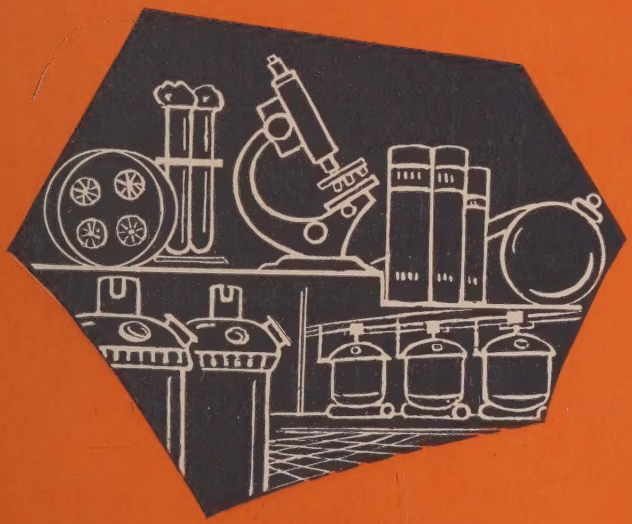
HINDUSTAN ANTIBIOTICS

Bulletin



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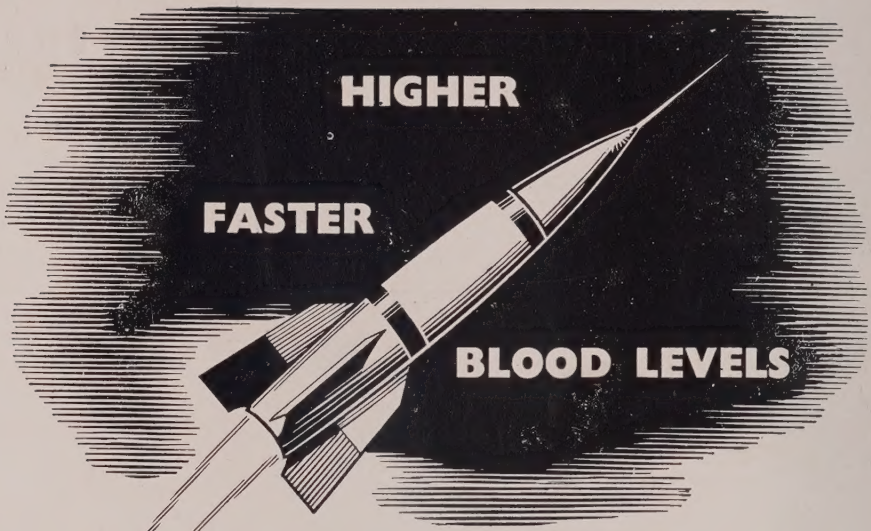

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HINDUSTAN ANTIBIOTICS

Bulletin

Vol. 1 **February 1959** **No. 3**

EDITORIAL & ADVERTISEMENT OFFICES

Hindustan Antibiotics (P.) Ltd., Pimpri, Poona Dt.

This *Bulletin* is published in February, May, August & November, and contains semi-technical articles and reviews on all aspects of antibiotics production and use.

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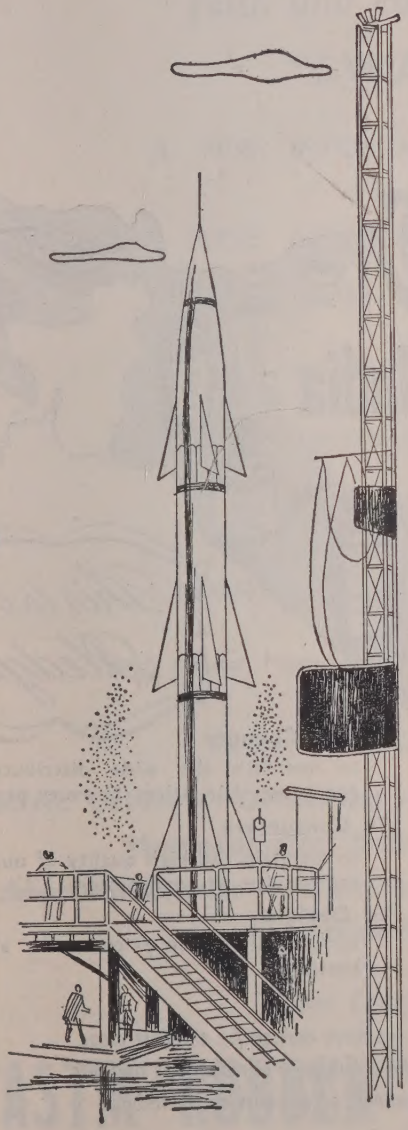

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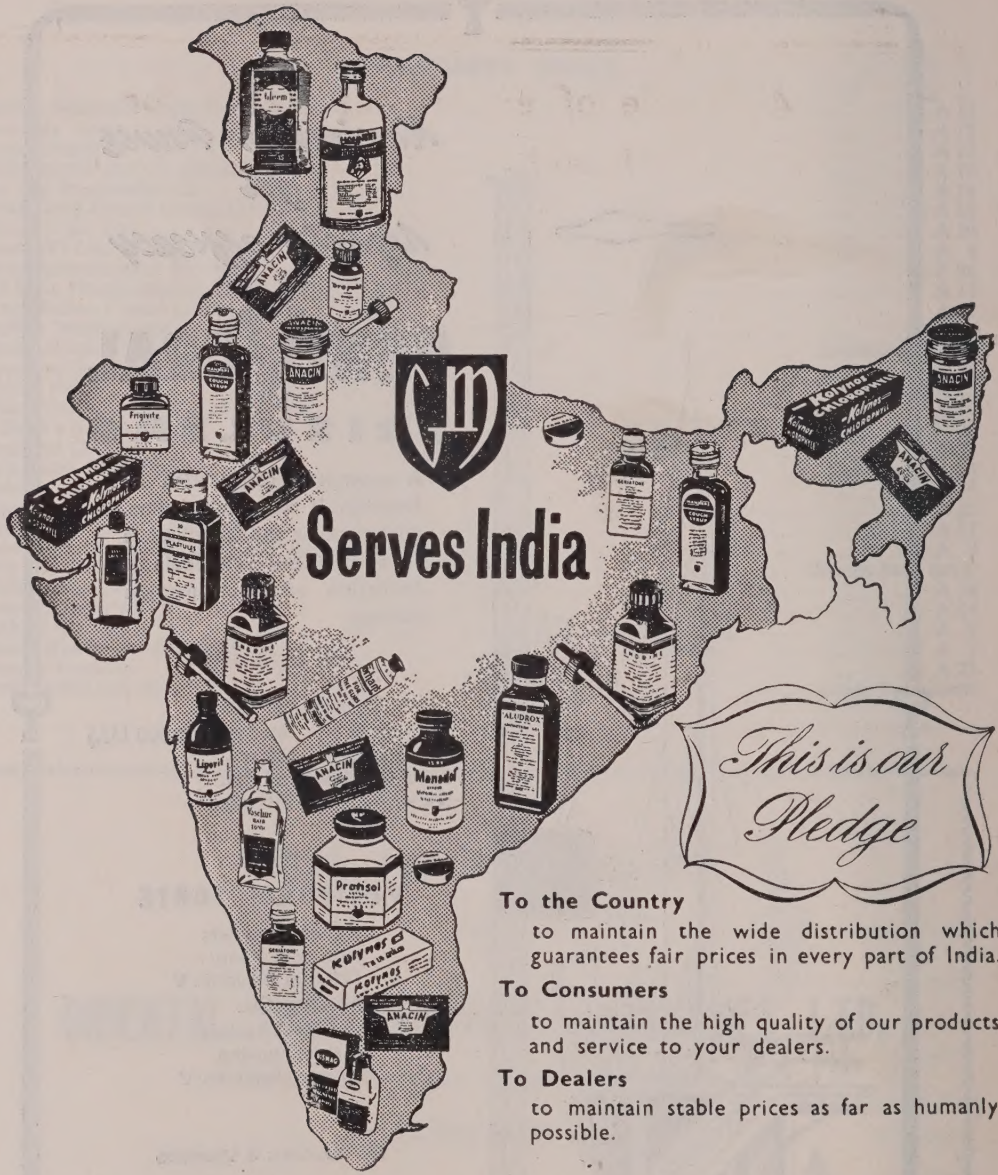

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Search for Antibiotics Against Cancer

Cancer is, in essential, a change in cell metabolism resulting in neoplastic growth. No satisfactory definition has so far been given, either regarding the nature of cancer or its inciting factors. Proliferation of groups of cells takes place without control, and such proliferated cells are characterised by lack of differentiation (anaplasia) and hyperchromaticity of the nucleus. The causes of cancer have long been shrouded in a veil of mystery and many physical, chemical, viral and hormonal agents have been attributed as incitants. While the benign tumours are not of much significance, the malignant tumours are real killers and cause considerable human suffering. The rapid cell divisions with several atypical mitoses and undifferentiated mass of tissue characterise malignant tumours.

With the advent of the antibiotics, interest was renewed in the possible cure of cancer by use of antibiotics. In the case of diseases caused by bacteria or fungi, the antibiotic could be used in killing or preventing further multiplication of the pathogens, without affecting the host. But in case of antibiotic therapy of cancer, the differential killing or suppression of division of the tumour cells alone has to be obtained. This cytostatic effect could only be brought about by suppression of the spindle formation during cell division, in short, by the anti-tumour substances acting as mitotic poisons. The surgical removal of tumours, radiotherapy, use of cytostatic chemicals, while still being used in the therapy of cancer, are rapidly giving place to antibiotic treatments. A brief survey of the lines of work taken up by various investigators in discovering new anti-tumour antibiotics would only reveal the intensive work that is being done in different laboratories with all the ingenuity in techniques.

For accurate testing of the anti-tumour substances, the tumor transplantation technique described by Loewenthal and Jahn as far back as 1932, is still being widely used. For large-scale screening of anti-tumour substances however, several *in vitro* testing methods have been devised which are constantly being improved upon by further studies. For observing the inhibitory effects of an anti-tumour substance *in vivo*, ascitic fluid containing cancer cells (usually Ehrlich's carcinoma) is inoculated intraperitoneally into mice and the inhibitory effect of the antibiotic is tested by noting the survival time of mice. In case of solid tumours like Crocker's Sarcoma 180, small tumour pieces are implanted subcutaneously in the axillary region of the mice by the trocar method. The inhibitory effects of the anti-tumour substance is determined by direct measurement of tumour size.

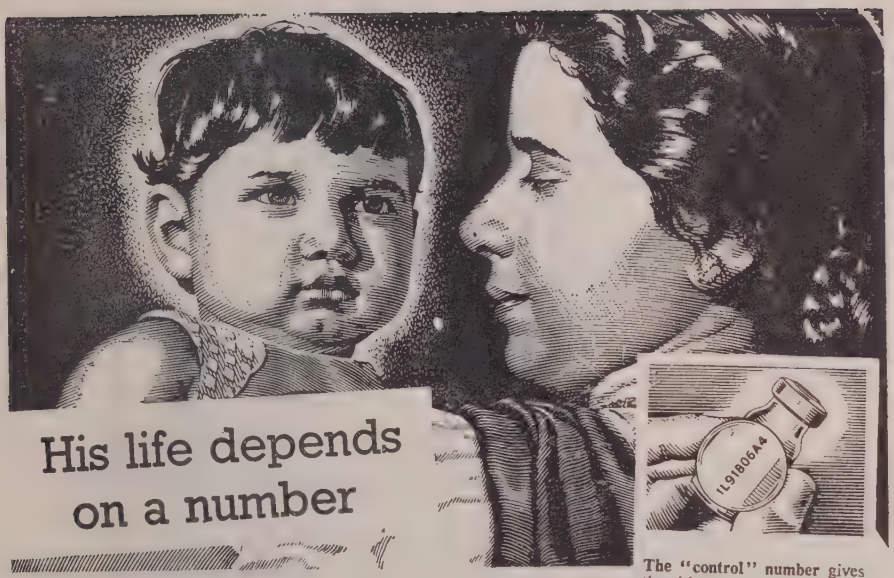
In preliminary screening of large number of substances for possible anti-tumour effects, it is not practicable to test all of them by *in vivo* methods. Several interesting techniques based upon some phenomenon which could be correlated with anti-tumour activity have been described and there is an intensive search for new methods. Yamamoto and Yamaoka described a chick embryo method using Yoshida sarcoma cells inoculated into the egg. The suppression of tumour formation on the allantoic membrane in the chick embryo cultures treated with anti-tumour substance was taken into account. Other workers noticed the suppression of cell divisions in the yeast *Kloeckeria brevis* or nonseptate filament formation by *Escherichia coli* as a test method for screening of anti-tumour substance. Amman and Safferman noted the suppression of cell

divisions in onion root tips treated with anti-tumour substances. Direct observations of the mitotic divisions in stained preparations was possible. Where there was a specific substance suppressing cell divisions, it resembled those seen in case of colchicine treatment. *In vitro* staining reactions in tubes using Ehrlich's carcinoma suspension has been described by Kikuchi and coworkers. *In vitro* contact between 2-3-5, triphenyltetrazolium chloride (T.T.C.) (with or without sodium succinate) and cancer cells gives a staining reaction which is prevented if an anti-tumour substance is present. This has been further developed into a cylinder plate method commonly used for assaying antibiotics. Using HeLa cells from tissue culture, or Ehrlich's ascites tumour cells from inoculated mice as test organisms, agar plates are poured. The substance to be tested is allowed to diffuse on agar and by using dilute solution of methylene blue, a circular blue zone is formed by the reducing activity of the cancer cells. This is due to the inactivation of dehydrogenase which is closely related to the vital functions of the cancer cells.

Another interesting line of work has been taken up by Gause. Based upon the observation that cancer cells have low rates of respiration, mutants of micro-organisms have been obtained which possess reduced oxidation uptake. (1/10 to 1/2000th of the parent cells). These mutants reveal the presence of anti-tumour substances when used as test organisms along with the parental strains. Recently Takaoka and others have even made use of a very interesting biological phenomenon. They found that substances that inhibit tumour cells also suppress development of ova of the round worms of hogs when tested *in vitro*. Making use of these correlation phenomena, methods for screening anti-tumour substances have been devised.

As regards the anti-tumour antibiotics, reported so far, most of them have been isolated from the culture filtrates of *Streptomyces* species except some, from fungi like, *Boletus edulis*, *Helminthosporium* sp. etc. These anti-tumour antibiotics have been mostly tested on mice and their action in suppressing one or the other type of cancer has been recorded. Caryomycin from *Streptomyces filamentosus* effective against Ehrlich's carcinoma was reported by Okami and Umezawa. The other antibiotics reported to be effective against Ehrlich's carcinoma are Gancidin from *Streptomyces* A.A.K. 84, Ractinomycin A and B from *S. phaeochromogenus*, Melanomycin from *S. melanogenes*, Sarkomycin from *S. erythrochromogenes*, Pluramycin from *S. pluricolorescens* and Actinoxanthine from *S. globisporus*. Some of them are active against sarcoma also (Yoshida sarcoma or Crocker sarcoma 180) in addition to their being effective against Ehrlich's carcinoma. Carzinocidin from *S. kitazawaensis*, Azaserine from *S. fragilis*, Carzinophilin A from *S. sahachiroi*, Mitomycin A and C from *S. caespitosus*, Raromycin from *streptomyces* sp. 314C, Aburamycin from *S. aburaviensis*, DON (6-Diazo-5-oxo-L-norleucine) from *Streptomyces* sp. P.D. 04997, Alazopeptin from *S. griseoplanus*, Puromycin from *S. alboniger*, Cellocidin from *S. chibaensis*, Actinobolin from *Streptomyces* sp. and Streptovitacin from *Streptomyces* sp., are some of the important ones.

As regards actual therapeutical value of some of these antibiotics in the treatment of human cancer, conflicting results have been reported with regard to Sarkomycin. Some of the Actinomycins which are highly toxic have been found to be quite effective when used in small doses. Actinomycin C appears to be a cytostatic medication of appreciable value in cases resistant to roentgenotherapy. Malignant conjunctival tumours have been reported to have been successfully treated with Actinomycin C. It may be reasonable to hope that in the near future antibiotics would be available for curing cancer diseases and to ameliorate the sufferings of mankind.



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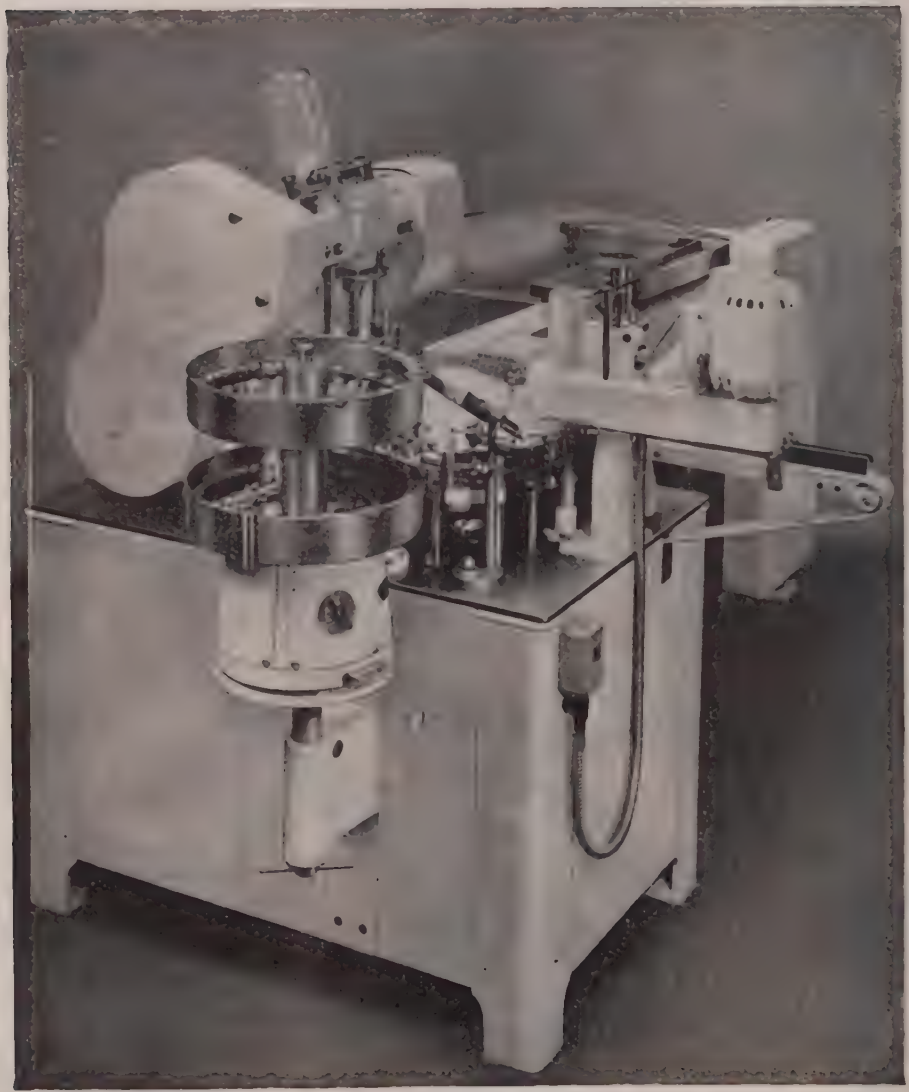

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Quality Control in Antibiotics Manufacture

Dr. P. D. Kulkarni, M.B., B.S., D.P.B.

Next to food, medicines are among the essentials for maintenance of the physical health and mental well-being of the people. Perhaps nothing of so great importance to human welfare is purchased more completely on faith than a bottle of medicine. The physician and the patient believes in the label implicitly and it is not possible for them to test the purity or dosage of the medicine purchased by them. Both the patient and physician must, therefore, be assured that they are getting medicine of highest quality as stated on the label, and that they need have no doubts about its purity, efficacy or safety.

Until recently, the main activities of most of the pharmaceutical manufacturers in India consisted of repacking of basic drugs or proprietary preparations imported from abroad, *i.e.* ampouling, capsuling, compounding, tabletting, etc. Some of the larger manufacturers imported the penultimate products and the last step in the manufacture was done here. Generally, these imports were covered by analytical reports from the laboratories of the respective foreign manufacturers and testing in local laboratories was confined to ensuring that no fresh impurities were introduced during the final processing and that the dose of the final product conformed to the declared dose on the label. However, with the production of fine chemicals and pharmaceuticals in India starting from basic raw materials, greater emphasis began to be laid on more elaborate and accurate analytical control of the products and compliance with prescribed standards. The Pharmaceutical Enquiry Committee (1953) rightly pointed out the inadequacy of testing facilities in India and the need to substantially improve the situation in order to win for drugs manufactured here, the confidence of the public in general and that of the medical profession in particular.

The Drugs Acts

The legislative provisions in the Central Drugs Act, 1940 and the Drug Rules made thereunder as well as the Drugs and Magical Remedies (objectionable advertisements) Act of 1954, are meant to ensure that only drugs of certain prescribed standards of purity, potency and safety, are put on the market by manufacturers. These Acts make it obligatory on the part of the producers to ascertain by appropriate tests that their products conform to the prescribed standards and to the labelled specifications before releasing them for sale. Standards of purity, quality, potency, identity, etc., and methods of testing are given in publications, which enjoy official and legal status, known as pharmacopoeias. Therein are also given the "limits of tolerance" as regards each specification to accommodate the unavoidable variations during manufacture and the errors in analysis. In India, latest editions of the *Indian Pharmacopoeia* (IP), the *British Pharmacopoeia* (BP), the *British Pharmaceutical Codex* (BPC), the *United States Pharmacopoeia,* (USP) and the *U. S. National Formulary* (NF), are all recognized by law.

In case of comparatively harmless simple medicines, testing of the final product might be quite sufficient. For special drugs a stricter control over every stage of manufacture including the testing of the raw materials might be necessary. Certain drugs are highly poisonous, while others

are dangerous if taken without doctor's supervision. In such cases, it is necessary to prevent self-medication by patients. Again, certain drugs deteriorate on storage and must be used within the prescribed time limit. For this purpose the Drug Rules classify the medicines under various schedules, requiring varying types and degrees of controls. Antiobiotics are included in the schedules C, C (1) and L. Schedule L drugs can be sold only against a doctor's prescription ; schedule C drug must have on its label, amongst other details, batch number, date of manufacture, date of expiry, etc. These controls are necessary in the interest of the patient.

Raw Material and Manufacture control

Manufacturer of Schedule C medicines (injectible antibiotics) is subject to control of the State Drug Control Authority as regards: (1) Hygienic conditions of factory buildings and premises, utilization of suitable machinery and equipment, and proper storage facilities. This is to prevent dust, dirt and germs entering the medicine during manufacture or the medicine deteriorating by being kept under unsuitable conditions of temperature and moisture. (2) Qualifications, health and strength of the staff and any changes in them. This prevents persons suffering from infectious diseases passing on the disease germs to the medicine under manufacture. It also prevents the unscrupulous manufacturer from dispensing away with his qualified staff after obtaining a manufacturing licence from the Drug Controller. (3) Provision of appropriate laboratories and equipment for control at various stages of manufacture. This ensures that the product is properly handled and processed at every step of manufacture. (4) Maintenance of prescribed records giving details of manufacture and tests applied to every batch, till two years after the expiry date of the batch. (5) Obligations to withdraw from the market any batch found not to conform to the prescribed and declared specifications. *The Acts thus ensure that antibiotics and other Schedule C drugs are manufactured under proper hygienic conditions from tested raw materials by specially qualified staff who are free from infectious and contagious diseases.*

Tests and Standards

Schedule C and L drugs include injectibles and these require extra-rigorous physical and chemical tests, special colorimetric, spectrophotometric, fluorimetric determinations and, in addition, chemical and microbiological assays, bacteriological tests, and animal experiments to check fever producing substances and toxicity.

Injectible preparations should be absolutely free from foreign particles like fibre, glass piece, hair, etc. This is checked by the clarity test. Particle size determinations and syringeability tests ensure that the dose will pass through the doctor's injection needle smoothly. Tablet size should conform to that prescribed in the pharmacopoeia. It should be easy to swallow, should not crumble easily under pressure but should disintegrate quickly on swallowing. These tablet qualities are checked by tests for tensile strength and disintegration time at controlled temperature. Weight variations are checked to ascertain that the bottle or tablet contains the specified and declared amounts of the drug.

Pyrogen test is performed by injecting the antibiotic in the ear vein of normal healthy rabbits and noting the rise in their temperature. It ensures freedom from fever producing substances. Safety test is performed on normal healthy mice by injecting the drug in their tail vein, and this test ensures freedom from abnormal toxicity. Histamine test is done on cats to ensure freedom from blood-pressure reducing substances.

In these animal tests, the animal receives, in proportion to its weight, a far larger dose

of the drug than is likely to be administered by the physician. Thus, these tests ensure that the drug is free from extraneous harmful substances and is fit for use as an injectible. For these biological tests a good animal house is essential for breeding laboratory animals under controlled conditions and by trained personnel.

An injectible should not contain any living germs, as these are likely to cause infection. Freedom from living micro-organisms is tested by sterility test. Many operations in testing and manufacturing have to be done in rooms which are under conditions of controlled temperature, humidity, sterility, etc. Continuous thermo-hydrographic records, serve as a check on the air conditioning. Bacterial plate-counts of petri-plates exposed in these rooms serve as a check on sterile air supply. Sterility of air in the main airducts can be checked by passing the air through nutrient broth.

Sterility tests are most exacting and are conducted by personnel well trained in rigid aseptic techniques. All operations on the sterile final product are done under strictly sterile and hygienic conditions, as trace contaminations may not always be detected in the final sterility test. Further, the manufacturer has to make sure that the product is bottled properly, especially if it is an injectible. The glass of the bottles and the rubber of the closures must not be of such material as would have a deleterious effect of the contents, even after a prolonged contact of three or more years. The seals should be such that no traces of moisture can pass through. Glass and rubber of poor quality may chemically affect the contents and cause deterioration. Fine chips of glass, and particles of rubber may get detached from imperfect vials. All these points need checking before a batch is ready for the market. The closures of multi-dose vials should be able to withstand 5 to 10 pricks of the injection needle. Keeping quality of antibiotics depends to a large extent on the efficient sealing of the vials. "Breathing" by vials increases moisture content of the drug. The product is bound to deteriorate on keeping, if the mouths of the vials are not of uniform size and if the rubber bungs do not fit in properly and also if the aluminium seals are not tight.

Representative samples of every batch are kept as "office copies" of the batch, and tested at regular intervals, say every three months, to make sure that the product has not deteriorated on keeping and that it complies with the prescribed standards till the end of the "expiry date" marked on the label. If a sample is found deteriorated, the sales section is immediately informed to withdraw the batch from the market and send for reprocessing.

If the expiry date for a particular injection of penicillin is given as three years, all manufacturing and testing protocols of it are expected to be preserved for over a period of five years at least. In fact, the expiry date limit is a conservative limit. Reputed manufacturers would make sure that their products maintain the quality and standard for a period longer than this limit. In the case of certain medicines, the Food and Drug Administration of United States allows an extension of the expiry date by one year or more, provided the manufacturer has protocols to show that his product does not appreciably lose potency over that period.

Conclusion

Products of the pharmaceutical industry—medicines—are not meant for use by normal healthy public, but by patients—sick persons with lowered vitality. These medicines must be of standard quality and the labels must speak the truth. It is to ensure this that the raw materials, processes and products of this industry are subject to so many checks and controls.

Mere analysis of final product is of not much significance. Final passing and release of a batch into the market means : the product has been manufactured by qualified persons using appropriate equipment, under hygienic conditions, from tested raw materials. It is only, in this perspective of rigid controls at every stage of manufacture that the testing of random samples from final products becomes highly significant. Close co-ordination and understanding between the men responsible for purchase, production, research, sales and quality control in the factory, is of very great importance for the best quality control programme. Close co-operation with the State Drug Control Authority is also essential. The need for precision analytical instruments and well-trained staff is greatly emphasized. Best results would be obtained where the quality control unit works independent of the production division as recommended by the Pharmaceutical Enquiry Committee. The quality control unit should also investigate complaints regarding substandard products, misbranding, deterioration in the quality or potency of the products before the expiry period. In all reputable concerns the quality control section keeps its internal standards far above those prescribed and performs special tests besides those given, in the pharmacopoeias. Storage studies are valuable in predicting shelf-life of the drugs, their deterioration properties and in furnishing useful information to the production, product development and research sections. In brief, therefore, the quality control unit is a guardian of the standards of quality of the factory's products and the people's health. It guarantees to the patients and to the physicians that their faith in the label on the bottle of the drug that they purchase is fully justified.

Untoward Reactions to Penicillin

Extracts from *Chronicle of the World Health Organization*, Vol. 12, pp. 295-301, September 1958.

World production of penicillin is now sufficient to provide more than 250 million courses of treatment annually. Against this staggering total, the number of severe reactions reported remains exceedingly small. Yet it is important that all users of penicillin should be fully aware of the reactions that may occur and of the precautions that should be taken to keep the risks to a minimum. With the aim of providing public health authorities with a readily accessible body of data on which to base their policies, WHO has undertaken a study of these questions.

Penicillin came into general use in 1943, but only two fatal cases from penicillin therapy were reported until 1949. During the past ten years, however, severe reactions have been reported with increasing frequency, and the number of fatal cases has multiplied rapidly. By 1957 it was estimated that some 1000 deaths from anaphylaxis due to penicillin had occurred in U.S.A. alone. The increasing frequency of reports of reactions in recent years is largely a natural consequence of the vast scale on which penicillin is now being used. Indeed, it is the general absence of untoward reactions that has encouraged such lavish use of penicillin. Unfortunately, it has also encouraged its indiscriminate use. Penicillin has been widely prescribed for all kinds of minor infections, and for conditions in which it is ineffective or not more effective than other drugs. Severe reactions occur only in patients sensitized by previous exposure to the drug, and it is known that many of the fatalities that have occurred following the legitimate use of penicillin have been attributable to previous unnecessary medication. Naturally, the chances of a patient having had previous treatment with penicillin are today much greater than they were 10 or 15 years ago.

Types of Reactions to Penicillin

Penicillin is an outstanding example among modern therapeutic agents with low toxicity. But these drugs are potential antigens, so that repeated administration may produce sensitization in the patient leading to allergic skin reactions or anaphylactic shock. Antibacterial drugs may also interfere with the metabolism of the microbial flora giving rise to superinfection and cross-infection by organisms less affected by the drug than others, or in a temporary exacerbation of symptoms due to the release of

noxious substances following microbial lysis. A more serious problem is the development of resistance in the organism against which the drug is being used.

Local and Systemic Toxic Reactions

These have not been a great problem with penicillin, particularly after the development of purer crystalline forms. Since the introduction of procaine penicillin with aluminium monostearate (PAM), local reactions have virtually ceased. There have been isolated reports of damage to the central nervous system, peripheral neuritis, and transient psychosis following intramuscular injection. Such cases are exceedingly rare, and the pathogenesis and nature of such reactions are also not clear. In contrast to the sulphonamides and many other drugs, penicillin does not cause damage to the bone marrow or haemopoietic system, and it can be safely given in severe anaemia. Intrathecal administration of penicillin causes meningeal irritation and serious complications have been reported, but this route of administration is seldom used to-day. It seems justifiable to conclude that "the toxic effects of penicillin in man, are, in the broad run of events, negligible. They certainly have detracted little from the use and usefulness of penicillin in clinical practice and public health programmes."

Allergic Skin Reactions

Penicillin can evoke the production of two types of antibody : a skin sensitizing antibody which can cause an eczematous reaction or an urticarial response, and an antibody responsible for anaphylactic reactions. Contact dermatitis caused by local application of penicillin in the form of ointment or solution, or by prolonged handling of the drug, as in doctors and nurses, is estimated to occur in 4 to 10 per cent of persons exposed to contact with the drug for long periods. It is, therefore, advisable to avoid local applications of penicillin whenever possible, and in any case not to continue treatment for more than three to five days. Desensitization is sometimes of value for doctors and nurses.

Parenteral administration or inhalation of penicillin can cause eruptions of the erythematovesicular type characteristically localized to the groins, the interdigital spaces, and the palms and soles. A previous fungus infection may result in cross-sensitivity, as it appears that such reactions may occur in persons not previously exposed to the drug.

Both types of eczematous reaction usually subside rapidly when penicillin is stopped and appropriate treatment given. Topical application of hydro-cortisone may be of value in prolonged cases. Generalized eruptions or exfoliative dermatitis rarely develop, and, if they do, they are generally of a mild type, although serious complications have been reported.

Serum - sickness - like penicillin reactions usually follow injections,

but can also occur after other forms of administration of the drug. They may appear within 30 minutes or only after several weeks. With modern preparations of penicillin, such as PAM, these reactions are estimated to occur in 1-2% of all patients receiving the drug. Serum-sickness-like reactions are not usually dangerous, but very rarely severe and even fatal complications may develop, such as larygeal oedema, periarteritis nodosum, purpuric lesions, or cardiovascular collapse. ACTH or cortisone may be life-saving in such cases. Mild reactions usually subside spontaneously within a few days or weeks when penicillin treatment is stopped. The antihistamines may be effective in severe or prolonged cases, but are of no value prophylactically. The enzyme penicillinase has given promising results in the treatment of urticaria and angioneurotic oedema resistant to other methods of treatment.

All forms of skin sensitivity to penicillin are usually transient, declining gradually over a period of 6-12 months. Nevertheless, treatment with penicillin should be avoided if possible in patients with a past history of skin reactions.

Anaphylactic Reactions

Allergic skin reaction to penicillin are rarely fatal ; most of the reported fatalities have been due to anaphylactic reactions which are only known to occur in persons sensitized by previous exposure to the antibiotic. Exceedingly small quantities of penicillin seem capable of causing sensitization in susceptible persons, but in most of the reported cases, however, the patients have had previously been exposed to amounts between 0·6 and 4·8 mega units.

The time interval between the administration of penicillin causing the anaphylactic reaction and the last previous administration is reported to vary from 10 days to 8 years. The length of the interval does not seem to bear any constant relation to the severity of reaction, which probably depends more on individual factors. In a sensitized person the first subsequent administration of penicillin brings on a reaction. Consequently, if a patient is given penicillin and no reaction occurs, it can be assumed that further administration in the same series will be without danger, provided that the intervals between the doses are not longer than four days. From this it follows that short courses of treatment with high single doses are preferable to longer courses with smaller doses. The type of penicillin preparation used does not appear to be important. Skin tests and clinical experience indicate that the common penicillin preparations are immunologically equivalent. Although most of the reactions reported have occurred with procaine-penicillin preparations, this merely reflects the fact that it is this type of preparation which is generally used.

The way in which a sensitized person will react to a subsequent exposure to penicillin is dependent largely on personal, constitutional

factors. Little is known as yet about the nature of these personal factors. The reactions occur most commonly in adults between 20 and 49 years of age, but are equally distributed between the two sexes. They are rare in children under 12 years old, and the frequency decreases with increasing age after 50. Children treated with penicillin are less likely to have had a previous exposure to the drug than older persons, but there is also some evidence that they are less easily sensitized. In the older age-groups, the consumption of penicillin is presumably lower than in younger adults, but it may be also that desensitization takes place in course of time. It seems to be well established that patients with a personal or family history of allergy are more easily sensitized than others, and that they react more severely to subsequent treatment.

Changes in the Microbial Flora.

Of the various types of changes produced in the microbial flora by the administration of penicillin, the development of resistance to penicillin in staphylococci has been of great concern. Resistant staphylococci can cause superinfection in a patient being treated with the antibiotic, or cross-infection in other patients in the same ward. The main problem has been created by staphylococcal pneumonias and urinary and wound infections. Staphylococcal enteritis may sometimes occur as a result of the superinfection of the bowel with penicillin-resistant organisms from the mouth or throat, but this complication is more common with the orally administered antibiotics.

The resistant organisms are spread by dust from clothings and bed clothes, or by hospital personnel who acquire resistant strains from penicillin-treated patients. Precautionary measures to prevent cross-infection in the hospital include isolation of staphylococcal cases and carriers, barrier nursing, and wearing of masks by hospital staff. The development of resistant strains can be minimized by restricting the use of penicillin to cases where it is absolutely necessary, and by giving sufficiently large doses at the beginning of the treatment to kill the organisms rapidly. Acquired resistance of the staphylococci is usually lost fairly rapidly when they are diluted in the general population, so that resistance is not met on a serious scale outside the hospital.

Superinfection during penicillin therapy may be caused by *Escherichia coli* and the paracolon and proteus bacilli as a result of either resistance or of decreased competition. *Candida albicans* overgrowth is comparatively less common with parenteral penicillin, though cases of moniliasis, usually in the mouth, have been reported. It has been suggested that the "broad spectrum" approach combining penicillin with other antibiotics may actually increase the risk of superinfection by all types of organisms.

In the treatment of syphilis with penicillin, a Herxheimer type of

reaction ("therapeutic shock") frequently occurs, and it is generally attributed to the release of noxious substances by the spirochaetes killed by the antibiotic. In early acquired syphilis, it occurs in 80-90% of patients. The reaction is usually mild in such cases and there is no need to discontinue treatment, but severe and even fatal reactions may occur in late neurosyphilis, cardiovascular syphilis, and gummatous syphilis, as well as in debilitated babies.

Like other antibiotics, penicillin may sometimes cause deficiency syndromes due to disturbance of the metabolic processes in the gastrointestinal tract and interference with the production of vitamin B complex and vitamin K. It is believed that the symptoms, which include black tongue and lesions of the oral mucosae, are due in part to an overgrowth of pathogenic flora.

Precautionary Measures

The frequency of severe reactions to penicillin can be greatly reduced by a number of simple precautions and it should be possible to eliminate fatalities almost entirely if the physician giving the injection always has at hand the necessary drugs to deal with an emergency. Before administering penicillin, the patient should be questioned carefully regarding previous exposure to the drug and any manifestations of an allergic diasthesis in himself or his family. If a reaction had occurred, renewed treatment with penicillin is contraindicated. Even mild reactions, such as itching, a tingling feeling in the tongue or fingers, a peculiar taste in the mouth, or slight fever, should be taken as an indication of the probable presence of an anaphylactic sensitivity, precluding reexposure to any type of penicillin preparation. An exception is the delayed type of serum-sickness-like reaction, which does not appear to be a usual precursor of anaphylaxis.

Patients with a history of asthma, hay fever, rhinitis, or other allergic diseases react more easily and more severely than others. Bronchial asthma, in particular, appears to increase considerably the risk of severe anaphylactic reactions in penicillin sensitized patients, and an asthmatic patient should not be treated with penicillin if this can be avoided. As an additional precaution a skin test can be performed, but patch tests are of value only in contact dermatitis. On the other hand, the immediate intradermal test, although usually positive in cases of anaphylaxis, may itself produce severe anaphylactic reactions. Moreover, a negative test does not necessarily exclude penicillin sensitivity. Routine skin testing is probably not a practical procedure for all patients, but might be considered before treatment of persons who routinely handle penicillin.

Penicillin should be injected slowly by the intramuscular route, and the patient watched carefully during the injection for any sign of a reac-

tion. If possible, the patient should be allowed to remain in the consulting room for about 15 minutes after the injection. Adrenaline (1 : 1000) should be at hand for immediate injection if anaphylactic symptoms appear ; if subcutaneous injection is ineffective, it may be given intravenously or even directly into the heart. Antihistamines like hydrabamine hydrochloride or tripelennamine, should also be given, and aminophyllin in cases of respiratory distress. These drugs, together with the appropriate syringes, should always be carried by the doctor giving penicillin injections. In clinics oxygen should be available, as well as a drip-infusion set. Continuous drip-infusion of *l*-arterenol or plasma has been recommended in cases of prolonged depression of blood pressuie. Intravenous cortisone or intramuscular ACTH is also indicated in protracted cases. For arresting anaphylactic shock 800,000 units intravenously, followed by 800,000 units intramuscularly of penicillinase is valuable.

Conclusions

When the reactions that penicillin may cause are set against the great powers which it possesses for control of communicable diseases, it is seen that penicillin does indeed do its task "with utmost efficiency and negligible harm," and there is ample justification for continuing to regard penicillin as "the queen of drugs." There is, however, need for education of doctors, nurses and the general public concerning the proper use of penicillin and the risk of sensitization, and the sale of penicillin should be restricted by the introduction of regulations regarding prescription. In mass campaigns, similar tactics should be adopted to those employed to overcome the problem of insecticide-resistance in the control of insect-borne diseases : the work should be intensified so that the value of penicillin can be exploited to the full before, or in case, sensitivity or microbial resistance makes its appearance.

Time is the one loan you never get twice.

You have time, plenty of time to heed health warnings when they occur. The slight scratch that does not heal, the wound that begins to fester are signs of trouble to come.

Heed these warnings. Don't waste time hoping for the best. Don't go seeking the advice of well-meaning but incompetent persons. Don't experiment in self-medication. Prompt and proper medical attention can avoid suffering, even tragedy. Time is on loan to you. Remember, the right time to see your doctor is the first time the danger signals occur. Later regrets will not bring back the right time.

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Selection of High-Yielding Strains in Penicillin Production

V. V. Bhatt, PH.D.

Among the various factors which have contributed to the development of penicillin production on commercial scale, none has influenced high yields as much as improvements in strains of the mold. The importance of this fact will be appreciated when one considers that there is very limited increase in yields by experimental changes in the medium constituents, temperature, aeration, agitation, or the pH. There seems to be a limit to the capacity of a strain of the mold for the biosynthesis of the antibiotic in submerged culture. From the stage of production of penicillin in milk bottles by surface culture in 1941, techniques have been developed for growing the mold in submerged culture in large fermentors thereby conserving space and time, and higher yields have been made possible principally by selecting improved strains by various mycological techniques.

Penicillium chrysogenum Thom, first isolated and described by Charles Thom, is a blue-green mold reproducing by means of conidia produced in chain. Unlike many of the species of *Penicillium*, *P. chrysogenum* does not possess sexual reproduction resulting in the formation of cleistothecia, but reproduces asexually by conidia. Work on changing the genetical character of the mold to obtain new high-yielding strains was started no sooner than the therapeutic value of penicillin was recognized and the demand for penicillin was ever increasing. Initial work at the Northern Regional Research Laboratories, Peoria, Ill., the Carnegie Institute and the University of Minnesota was soon followed by intensive work at the University of Wisconsin by Backus and Stauffer in collaboration with a number of students. In a recent review of their work for the last ten years, an account of the several lines of investigation taken up during the period is given. It is a matter of great pride and credit for them that the high yielding strains developed by them are used in most of the industrial concerns as the parental stock for further selection work.

As already stated *P. chrysogenum* reproduces only asexually by means of conidia and hence breeding of high yielding strains in the sense of crossing two parents, known among higher plants, is out of question. The conidia are one-celled, mostly uninucleate although cases of multinucleate conidia have been reported.

Strain improvement may be obtained by changing the genetic or hereditary patterns influencing the efficiency of biosynthesis of the antibiotic. In changing the genetical characters of the mold several physical and chemical mutagenic agents have been used with varying degrees of success. Mutation is a true breeding change effected in the germ plasm. In gene mutation the particular gene in the chromosome is affected and the resulting change in the phenotypic characters may be morphological or physiological. In the case of more profound changes like fragmentation and deletion of chromosomes, or inversions and translocations of the chromosomes, the phenotypic characters are also altered markedly. The changes in the gene pass on to the descendants normally by division of the nucleus with subsequent spore formation. Each nucleus of the individuals perpetuates the changed charac-

teristics which in turn affect the metabolic behaviour of the organism.

In the selection of strains the principal factors taken into account are high penicillin yield in the shortest period of time using minimum amount of raw materials. The raw materials taken into consideration are the sugars and the precursor. For selection to be effective there should be a population showing variability. Many of the high yielding strains have been selected from colonies showing natural variation. These variations involve either the entire colony or, sometimes, sectors. When they are true breeding they are referred to as gene mutations, though in many cases variations observed are due to changes in growth conditions. These 'dauer modifications' are of common occurrence.

Natural variation is a very slow process but can be accelerated by physical agents like x-or γ-radiations, or ultra violet light, and by chemicals like the nitrogen mustards. Various other physical and chemical agents have also been used but their effects are of a doubtful nature since natural variation itself manifests phenotypic changes. Techniques employed for induced mutations by ultraviolet or by chemicals are well described in textbooks. Essentially these consist in the preparation of spore material of a genetically pure strain isolated with the micromanipulator and microscope or obtaining well separated colonies by plating spore suspensions in sufficiently low dilutions. The spore material is then treated with the mutagenic agent for a predetermined time. About 5 to 10 per cent survival rates are maintained after the treatment.

Having selected large number of the surviving colonies which are considered to be mutants, the next stage is their evaluation for penicillin production. Morphological mutants are easily recognised by differences in growth characters and sporulation. From a green-spored form it is not unusual to obtain strains having brown, yellow or white spores. Many colonies may remain without sporulation. Each colony is transferred on to agar slants and tested in shake flasks for penicillin production in submerged culture. Replicate trials are run according to plan of the experiment and the high-yielders are finally selected for testing on a pilot plant scale. Large scale testing is limited by the space on the shaker as well as by other facilities. However, it is important that the complexity of the assay method should not be such that it will, because of the time taken for performing it, reduce the number of isolates that can be tested.

Attempts have been made by numerous workers to reduce the number of strains to be tested on the shaker by evaluating the penicillin yielding capacity of the strains before selecting them for shake flask tests. Raper, Alexander and Coghill grew colonies on agar in petri plates and cutting uniform-sized blocks, tested them against *Bacillus subtilis* for antibacterial activity. Depending upon the size of the zone of inhibition, the relative yields of the strains were evaluated. Thirumalachar *et al.* used as the test organism *Xanthomonas malvacearum* which causes the black arm disease of cotton. This bacterium is sensitive to penicillin only at concentrations above 500 to 1000 units, so that most of the low yielders could be eliminated on the petri plates. The number of mutants selected for the shake flask tests are, therefore, considerably reduced.

Recent studies by Pontecorvo and colleagues on the parasexual cycle among Fungi Imperfecti have opened new lines of work in breeding strains for high yields of antibiotics. It has been found that among fungi which have no sexual reproduction the hyphae from two different colonies often fuse or anastomose resulting in effect to that produced in sexual reproduction. These cells containing the nuclei from two

parents are termed heterokaryons. Often these two nuclei fuse and form what is called a heterozygotic diploid, which in fact would represent a true breeding hybrid produced by parasexual combinations. While considerable work has been done on the theoretical aspects of heterokaryosis and related phenomena, as yet no improved commercial strain has been obtained with this technique for penicillin production.

After obtaining a promising strain its maintenance for use in commercial production is very important. Cultures when maintained for a long period on artificial media, produce saltants which adversely affect penicillin yields. Therefore, lyophilized and soil cultures are maintained as master cultures. Periodic tests are made to ensure the viability and antibiotic yielding capacity of the strain.

Antibiotics Information

Trends in Antibiotics Production

(III)[1] EASTERN EUROPE, MIDDLE EAST, SOUTH AFRICA

U.S.S.R.

Under her fifth five-year plan (1951-55) Russia had planned to raise the output of drugs and medical equipment at least 2-1/2 times the production in 1950, and this is reported to have been achieved also in antibiotics manufacture. Some antibiotics like bacitracin and viomycin are still imported, but import of drugs in general, has now been greatly reduced and concerted efforts are being made for achieving self-sufficiency, overcoming the difficulties and delays encountered at earlier stages, and raising the standard of drugs including antibiotics. Since 1954 much work has been done in the production and preparation for clinical use of a number of antibiotics like penicillin and its preparations, streptomycin, levomycetin (l-chloramphenicol), sintomycin (chloramphenicol), viomycin, tetracycline, tetramycin, colimycin, flamycin, actinoidin, ecmolin, albomycin, inamin, the anti-dysentery "antibiotic No. 16" and salts of usnic acid. The supply of pharmaceuticals improved, and the retail price of medicines dropped by almost 700 million roubles during 1951-54, with concurrent improvement in the quality of the products. The output of the chemical pharmaceutical industry registered a three-fold rise, the increase in penicillin and streptomycin production being particularly noteworthy. The output of ampoules rose from 212 million in 1950 to 572 million in 1955, and the output of prepared medicines increased from 291 million to 696 million units during 1951-55. It is reported that, in general, new technological processes, expansion of plant facilities, mechanization and reconstruction of several divisions of the factories, helped to raise the production, lower expenditure on raw materials, increase the productivity of equipment and labour and reduce production costs. The Riga factory for Medical Preparations, the Moscow chemical-pharmaceutical factories "salicyloviy," "im Karpov," and "Akrikhim" were named among the best of the pharmaceutical firms.

A method for isolation of vitamin B_{12} from antibiotic fermentation wastes was developed, and several new antibiotics such as ecmolin (an antibiotic from fish) noted to have effective synergistic action with penicillin, streptomycin and tetracyclines and also considered useful against resistant microorganisms, actinoxanthine, cerulomycin, heliomycin, aurantin, secacin, sapropelmycin, sapromycin, neocide, and erythrin from human red blood corpuscules effective against diphtheria bacillus, were reported. It is quite possible that some of these compounds are identical with known antibiotics. A method for production of levomycetin from styrol, saving 4 million roubles at the Karpov factory alone in 1956, synthesis of dihydrosarcomycin (an analogue of the antitumour antibiotic sarkomycin), industrial production of mycerin, cyclomycin and biomycin, and selection of high-yielding strains of *Penicillium*, were also successfully carried out during the period.

For the sixth five-year plan (1956-60), the directives of the 20th congress of the CPSU stipulated a two-fold increase in pharmaceutical production on what was

(1) Part (I) covering U.S.A., Latin America and Canada appeared in V. 1, No. 1, p. 45, and Part (II) covering U.K., and Western Europe in No. 2, p. 71, of this *Bulletin*.

obtained in 1955. Capital investment will be 3 times that for 5th plan. Production of nearly a hundred new medicinal preparations including eusintomycin for treatment of dysentery in children, is envisaged under the scheme. Three new plants are to be set up, one of which is expected to start production by the end of the plan period. Important steps which are reported to have been taken with a view to implement the directives for the pharmaceutical industry are installation of automatic and semi-automatic equipment and mechanization wherever practicable and economical, extension of existing plant facilities, exchange of information between similar and contiguous plants and utilization of experiences in other branches of the industry and achievements of other countries. During the first half of 1956, some factories fell short of the plan targets but in others the achievements are reported to be substantial, for instance the output of chloramphenicol was up by 72 per cent and medicine in ampoules by 24 per cent in comparison to the corresponding period in 1955.

In eastern U.S.S.R. the pharmaceutical industry is developing gradually. During the fifth plan, production in east and west Siberia nearly doubled in comparison to 1950. Considerable investments are to be made in the Anzhero-Sudzhensk, Irbitsk and Kemerovo plants.

Czechoslovakia

The Czech pharmaceutical industry is fairly well established, producing sulphonamides, PAS, penicillin, streptomycin, chloramphenicol and other drugs. The Roztoky penicillin plant was established a decade ago and the drug is now on the country's export list. In 1956 a second and larger penicillin plant of Soviet design and equipment, in the village of Slovenska Lupca, started production. Construction of the plant was begun early in 1955 and large scale manufacture of penicillin preparations including procaine penicillin, began in mid-1956. Future developments in the plant include production of streptomycin, oxytetracycline, antibiotics for foodstuffs and agricultural use.

The antitubercular antibiotic, D-4-amino-3-isoxazolidone (cycloserine), was synthesized in 1956 in the Chemical Institute of the Czechoslovakian Academy of Sciences. By the end of the year, the drug was on large scale manufacture, a short cut six-step for its production having been developed. In the same institute in 1956, chloramphenicol and dihydrochloramphenicol were synthesized and processes for their mass production worked out. Produced on a large scale are penicillin and its various preparations, chloramphenicol, oxytetracycline, and mixtures (Piracillin tablets, Polbicillin). Under production are chlortetracycline, tetracycline, erythromycin, streptomycin and dihydrostreptomycin. A number of these items are exported.

Poland

Good progress is credited to the Polish pharmaceutical industry in the last decade and penicillin and its preparations are major items in the country's export list. The reported overall increase of 700-800% in production includes synthetic chloramphenicol. Streptomycin and chlortetracycline production is not yet sufficient to meet home requirements. For expansion of the antibiotic industry during the current five-year plan, three plants have been purchased from the U.S.S.R. One of these is set up in Tarchomin (near Warsaw), the second in Krakow and the third in Pablanice (near Lodz), and all the units are expected to begin operations by mid-1959. In the Pablanice plant for hypotensive drugs, a division is set apart for chlortetracycline. Oxytetracycline is to be produced in another year or so in a separate plant. Sixteen new products including chlortetracycline and vitamin B_{12} are on the current Polish drug manufacture programme.

Product	Unit	1949	1953	1954	1955	1956
Pharmaceuticals	Mill. Zloty	68.7	400.5	572.0	831.8	
Antibiotics	„		47.0	95.9	131.0	
Penicillin	Mill. Units		2,329.9	4,679.0	6,238.8	7,932.6
Chloromycetin	Kg.		372.0	806.0	1,191.0	

Hungary

The Hungarian pharmaceutical industry which had made noteworthy contributions in the field of alkaloids, vitamins and sulphas, has achieved fast recovery after the war. Produced on a large scale are antibiotics, the sulphas and vitamins among others. Hungary has now plans to raise the production of drugs twenty-five times by 1965 compared with 1949. For this purpose reconstruction and expansion of three of the biggest drug factories *viz.*, the United Drug and Food, the Chinoin, and the Kobanya, has already started. The most important undertaking in the field is the Chinoin factory in Budapest (founded 1910), now producing penicillin, streptomycin and chloramphenicol. The United Drug and Food is marketing among other things, two new long-acting penicillin depot preparations, Retardicillin and Promptcillin. The penicillin plant in the Moldau region uses Soviet equipment and is claimed to be a very attractive plant. The pharmaceutical works of Hajdusag has been another important antibiotics manufacturing centre. Penicillin products are on Hungary's export list which contains some 125 medical and veterinary preparations.

Yugoslavia

The penicillin production unit of the chemical-pharmaceutical factory "Galenika" in Zemun near Belgrade has been renovated to produce 4 tons of penicillin annually, marking a ten-fold increase over the output in 1945 when the plant started operations. The factory employs over 1,000 people. The largest proportion of the penicillin preparations put out is Jugocillin (procaine penicillin G 300,000 i.u. and potassium penicillin G 100,000 i.u., in 2 mil. ampoules), only 5% of production being crystalline potassium penicillin. Streptomycin which is now imported, would soon be the most important product of the factory and it is planned to produce 10 tons of it by 1961. Laboratory work in this connection has already started. "Galenika" together with the "Pliva" pharmaceutical works at Zagreb accounts for over 81% of the pharmaceutical production in Yugoslavia. The "Pliva" factory is reported to produce Geomycin, an antibiotic of low toxicity, active against gram positive and gram negative organisms, viruses and protozoa, and effective where other antibiotics have failed. There is also the penicillin plant equipped by UNICEF which is stepping up production. Exports of antibiotics like penicillin and chloramphenicol started in 1957. During that year Yugoslavian exports of pharmaceuticals increased by 17% over what was in 1956, Sweden, Switzerland, Federal Republic of Germany, Austria, U.K., etc., being the major importers.

Rumania

The country's first penicillin factory at Jassy started production in December 1955. It is of Soviet design and uses Soviet equipment, and construction took three years.

This is reported to be one of the largest antibiotic plants in South-East Europe producing enough penicillin for export since 1956. In addition to procaine penicillin, dipenicillin and other formulations, the firm produces Reticillin a new antibiotic of the penicillin type for treatment of certain pulmonary diseases. Chlortetracycline production started late in 1957. Chloramphenicol, streptomycin and oxytetracycline are to be taken up shortly. A large and up to date penicillin plant is coming up in Moldavia.

Bulgaria

Next to fertilizers and soda, pharmaceuticals are the most important industry in Bulgaria. Sulphonamides, vitamins, hormones, alkaloids, antibiotics, are all mass produced. The penicillin factory near Razgrad, opened towards the end of 1954, manufactures enough penicillin for export. Streptomycin and chlortetracycline are other antibiotics produced on a commercial scale. Crude penicillin and other pharmaceuticals are on Bulgaria's export list.

Turkey

Near Istambul, E.R. Squibb and Sons are building a factory for the manufacture of penicillin, streptomycin and other pharmaceuticals. Abbott Laboratories unit in Istambul, opened in 1956, is in full operation. Two years ago, Chas. Pfizer also announced new plants in Turkey. Since 1956, the German firms Farbenfabriken Bayer A.G., of Leverhusen, E. Merck of Darmstadt, Kroll A.G., of Ludwigshaven and Schering A.G., of Berlin, are building up a large factory near Istambul for manufacture of specialized pharmaceuticals and proprietary products. A substantial amount of Turkish capital will be used in their undertakings.

Egypt

Prior to 1952, almost all pharmaceuticals were imported into Egypt. During the last five years there has been gradual progress in industrialization to meet local requirements by indigenous manufacture. The government has encouraged and granted facilities to local private companies for expanding their resources and increasing output. The value of all drugs and medicinals produced locally amounted to £586,359 in 1953, £734,395 in 1954 and £866,677 in 1955. Penicillin-streptomycin, chloramphenicol and the tetracyclines are still imported.

In 1956 U.N. technical experts had discussions with the Egyptian productivity council on matters relating to the expansion of the pharmaceutical industry in the country. A penicillin plant has been set up in Cairo with Russian aid. The Five-year industrialization plan for Egypt specifies establishment of half a dozen new pharma-

Egypt : Production of Antibiotics

	1954	1955
In bottles ..	1,095,536	1,598,290
Tablets ..	400,000	197,000
Kgs.	2,880	2,260

Egypt: Import of Pharmaceuticals

	1954		1955	
	Kgs.	£	Kgs.	£
Pharmaceuticals and vitamins	3,230,566	5,179,210	3,550,629	5,727,392
Antibiotics..	132,499	392,690	243,477	524,814

ceutical firms. Under a credit agreement with Russia the laboratories and factories are to be set up with Russian equipment and technical assistance. This credit agreement of 700 million roubles specifies among a number of undertakings a pharmaceutical factory to produce 100 tons of sulphas, 2.5 tons of chloramphenicol and 156 tons of salicyclic compounds per annum ; and also an antibiotic factory for 4 tons of penicillin, 2.5 tons of streptomycin and 25 tons of dextran per annum, with provision for increasing the capacities later.

Israel

Israel is reported to have exported crystalline penicillin to Rumania as early as 1950. The penicillin was produced by a Jerusalem laboratory which was expanded later. The country's pharmaceutical industry which supplied some of the medical needs of the Allied Forces in Middle East during World War II is now being expanded to meet greater part of the local requirements. There are about twenty small and medium sized plants and laboratories producing vaccines, antibiotics, vitamins, hormones, etc., in various formulations valued at about $1.5 million. Raw materials used are either imported or those available locally. In 1954 export of crude and prepared drugs was about 10 per cent of total production. In the new development centre of the Neger town of Ashdod on the Mediterranean coast a pharmaceutical factory is being set up at a cost of Is. £2.5 million with private American capital investment. Israel's pharmaceutical export is expected to go up steeply when this plant goes into production.

Syria

The Syrian Ministry of Health is planning a £3.5 million factory for pharmaceuticals principally penicillin, streptomycin and insulin. So far the drug industry was centred in the hands of the Damascus firm Societe des Produits Pharmaceuticals et Industriels S.A., processing vegetable drugs.

Iraq

In March 1958, Iraq's first pharmaceutical factory was inaugurated by King Feisal. The Bagdad factory built by Iraqi pharmaceutical Company under the supervision of, and technical assistance from, Union Chimique Belge, has three departments. The first has an annual production capacity for 300 million tablets, the second for 80 tons of medicinal ointments and 300,000 litres of syrups, and the third for filling 25,000 ampoules a day. The Iraqi Pharmaceutical Co., was established in 1954 by Iraqi doctors, pharmacists and industrialists. The company manufactures certain pharmaceutical specialities under license from the Belgian Company and two other English firms while other items are sold under the firm's own labels. The new factory comes within the Iraqi Government's statute for promotion and expansion of industry and, therefore, enjoys tax and duty dispensations for the first ten years of production.

Iran

Under a contract entered with the Imperial Welfare Organization (*Darou Pakhsh*), Allen and Hanburys Ltd., will set up a pharmaceutical factory near Teheran at a cost of about £1 million. Items to be produced by the factory include a wide range of parenteral solutions, tablets, ointments, etc. The British Company will provide technical experts and the design and also train up Iranian students in their U.K. plant. *Darou Pakhsh* will provide the capital and also arrange to distribute free of charge the products to the various Imperial welfare organizations. A greater part of the production will, however, be put on the open market. The agreement is for 15 years, but may be extended.

South Africa

Large scale production of penicillin started towards the end of 1953. One plant operated by a firm (producers of acetates, methylated spirit, vinegar) in Germiston, Transvaal, works in collaboration with

Distillers Corporation Ltd., of U.K. Another factory near Pietermaritzburg, Natal, set up by a firm manufacturing veterinary drugs, confines its production to penicillin for veterinary use.

Allen and Hanburys (Africa) Ltd., at Congella, Durban, have built new laboratories in their research and control department to extend the facilities for antibiotic assay, microbiological and similar work.

Abbott Laboratories, Wyeth Laboratories and the Schering Corporation of the United States are important exporters of pharmaceutical raw materials to S. Africa. The United Kingdom is next in line.

Belgian Congo

Union Congolaise des Produits Chimiques et Pharmaceutiques (Unipharma) in Belgian Congo are well known pharmaceutical manufacturers in the region.

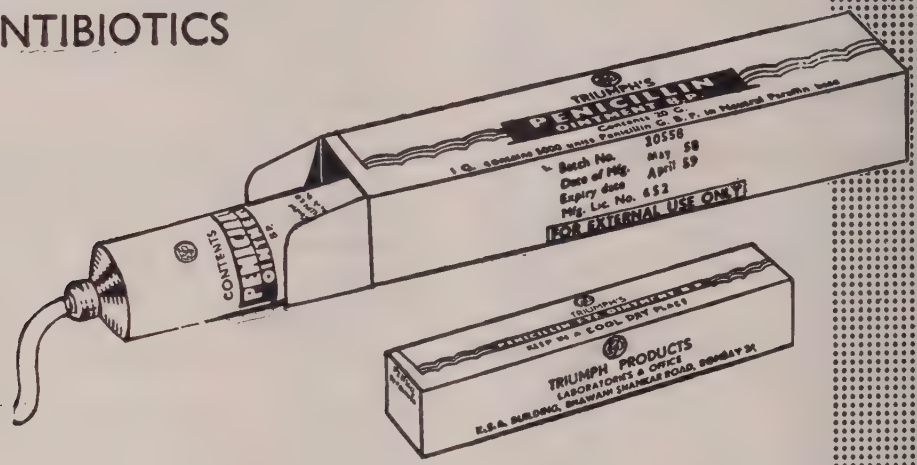
Hoescht S. Africa in Leopoldville, Belgian Congo, imports pharmaceuticals and dyestuffs from the parent company in Germany.

A.N.

ERRATUM

V. 1, No. 2, p. 62, last paragraph, line 3.—*For* "As such during fermentation" *read* "As such penicillin yield cannot be dramatically increased by feeding these amino acids during fermentation."

A FURTHER STRIDE IN
MANUFACTURE OF PHARMACEUTICALS
& ANTIBIOTICS



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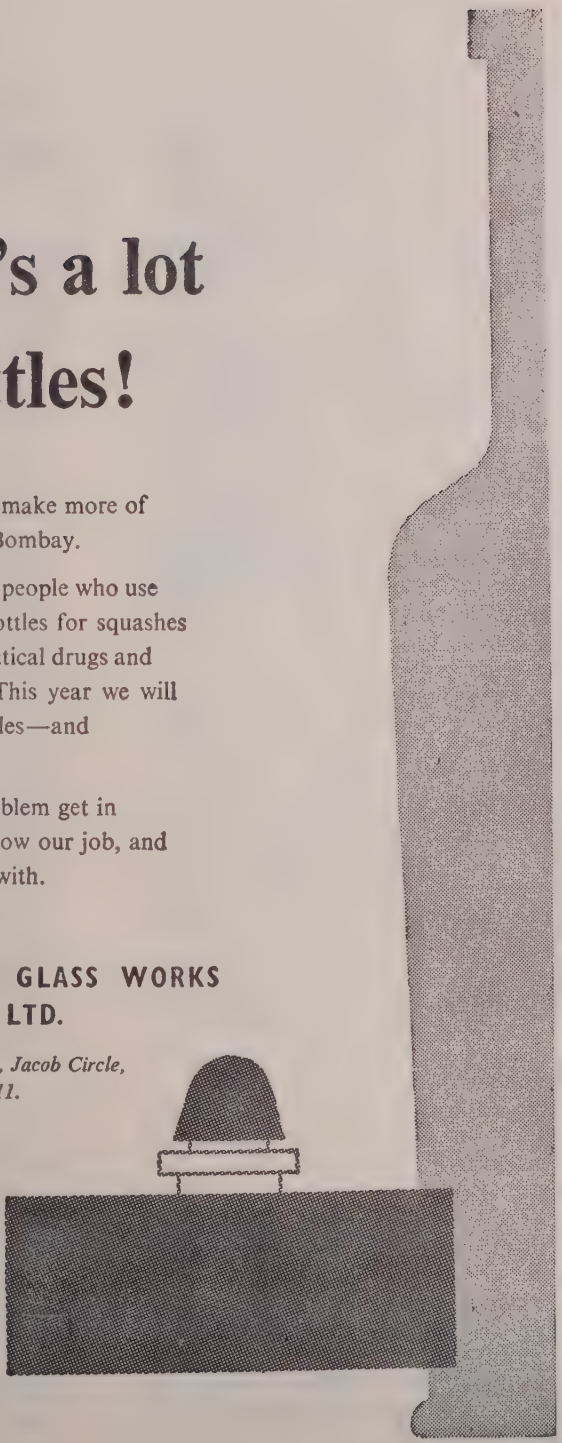

H. A. Notes

Lt. Col. Jaswant Rai Dogra, M.D., Ch.B. (Edin.), D.T.M. (Liv.), I.M.S. (Retd.)—Lt. Col. J. R. Dogra, former Managing Director of this Company, passed away at Queen Alexandra Hospital, London, on 8th November 1958.

Born in Hoshiarpur (East Punjab), June 9, 1903, in a family of engineers and doctors, Col. Dogra was educated at the Government College, Lahore and received the Diploma in Tropical Medicine from Liverpool School of Tropical Medicine and his Doctorate in Medicine from Edinburgh University in 1929. He was commissioned to the Indian Medical Service in 1929 and soon after posted in the North West Frontier. He was called to the Medical Research Department of the Government of India, assigned to Haffkine Institute as assistant director in 1935, then at Central Research Institute, Kasauli, and later at King Institute, Guindy between 1938-40. During World War II Col. Dogra was in Persia and Iraq (Paiforce), where he held high administrative posts. Returning to India, he took charge of the large training centre of the Indian Army Medical Corps in Rawalpindi and then was back at the Haffkine Institute as assistant director, 1946-54, in charge of the vaccine and other divisions. His publications include some 35 scientific papers, two books and eight training pamphlets on miscellaneous administrative and medical topics. He was appointed Managing Director of this Company in 1954 and he retired in December 1957. During his tenure he tried to serve the Company to the best of his abilities and his sad demise is mourned by all his friends and admirers.

Dr. Ganapathi Sankaran, M.B.,B.S.—Dr. G. Sankaran, former Works Manager of this Company, passed away on 18th December, 1958, at Calcutta.

Born in Masulipatam, December 15, 1900, Dr. Sankaran, graduated from the Presidency College and Medical College, Madras, in 1925. After working with Dr. Newcombe in the office of the Chemical Examiner with the Government of Madras for two years, he was appointed Biochemist at the Nutrition Research Laboratories, Coonoor, in 1928 where he did important work in the field of biochemistry and rabies. He spent a year (1932-33) at the Cavendish Laboratories, Cambridge, on an I.R.F.A. fellowship. Returning to Coonoor he specialized in tissue culture work. He joined the Biochemistry department of the Hygiene Institute, Calcutta in 1938 and retired as Professor of Biochemistry and Nutrition, in December 1955. During the Bengal famine of 1943, he did very valuable work in the field of nutrition, and soon after he was ready with a blue print for an integrated chemical industry for India. During his tour abroad in 1945-47 he gained considerable American know-how of the mass production methods of vitamins and antibiotics. In October 1950 he was transferred from the Health Ministry to the Ministry of Production and appointed executive head of the Indian Penicillin Committee, the forerunner of Hindustan Antibiotics.

All through the period of his service in this Company, Dr. Sankaran was closely associated with the research and production problems relating to the manufacture of penicillin. Dr. Sankaran was a blend of a chemist, chemical

engineer, biochemist and a medical man, with a flair for engineering right from his early days. Simple in habits, he commanded the respect and admiration of all who knew him.

Production and Sales.—The calendar year 1958 registered a 51 per cent increase over the 1957 figures in the quantity of penicillin certified and passed, *i.e.* 26.92 m.m.u. in 1958 against 17.8 m.m.u. in 1957. Gross sales during 1958 was Rs. 304.99 lakhs compared to Rs. 124.68 lakhs in 1957.

Darwin-Wallace Centenary.—Under the auspices of the Science Seminar of this Centre a series of five lectures were delivered during September-December 1958, celebrating the Darwin-Wallace Centenary. The principal speakers were Dr. J. H. Crooke (Evolution and animal behaviour), Prof. T. S. Mahabale (Neo-Darwinism), Dr. M. J. Thirumalachar (Historical aspects of organic evolution and the origin of species), Dr. K. Ganapathi (Philosophical implications of Darwinism), and Dr. K. S. Gopalkrishnan (Life and works of Charles Darwin).

On January 24, Shri A. B. Pant, Political Officer in Sikkim and Bhutan, gave an informative and thought-provoking talk on the subject "Our N. E. Frontier."

Drugs Group Meets.—The Drugs Group of the Development Council for Drugs, Dyes and Intermediates and Members of the Indian counterpart of the Russian Team of Pharmaceutical Experts, met at Pimpri on 20-21 November 1958, for discussion of the plans for expansion of the drug industry in India.

Ace Cyclist.—Shri Tukaram Motiram Rajput of the Store Section won first place in the Annual Bombay Poona Cycle Race held in December, 1958. He was the recipient of a number of trophies for his splendid performance.

January 26, 1959.—Republic Day was celebrated with due festivity. Sunday, the 25th, was a day of sports and athletics suitably rounded off with the annual social gathering of colony residents, fancy dress competition, and exhibition matches. On 26th morning, the Managing Director hoisted the national flag in the factory and later at the Welfare Centre in the colony, followed by distribution of sweets to children. The evening provided full fare of entertainment, dances, music, humorous skits, etc.

HINDUSTAN ANTIBIOTICS BULLETIN

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INSTITUTION OF CHEMISTS (INDIA)

ASSOCIATESHIP EXAMINATION, 1959

The Ninth Associateship Examination of the Institution of Chemists (India) will be held in November, 1959. The last date for Registration is 31st March, 1959. The examination in Group A (Analytical Chemistry) is divided into the following ten Sections and each candidate will be examined in two of them according to his choice as approved by the Council, in addition to the General Chemistry including Organic, Inorganic, Physical and Applied Analytical Chemistry—(1) Analysis of Minerals, Silicates, Ores and Alloys ; (2) Analysis of Drugs and Pharmaceuticals ; (3) Analysis of Foods ; (4) Analysis of Water and Sewage ; (5) Biochemical Analysis ; (6) Analysis of Oils, Fats and Soaps ; (7) Fuel and Gas Analysis ; (8) Analysis of Soils and Fertilisers ; (9) Analysis connected with Forensic Chemistry ; and (10) Analysis connected with Leather Chemistry. The Examination is recognized by the Government of India as equivalent to M.Sc., for purposes of recruitment of Chemists.

Further enquiries may be made to the Honorary Secretaries, Institution of Chemists (India), Chemical Department, Medical College, Calcutta 12.

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